Epigenetic memory in induced pluripotent stem cells.

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Public Summary:
Adult cells that have been reprogrammed into induced pluripotent stem cells (iPS cells) do not completely let go of their past, perhaps limiting their ability to function as a less controversial alternative to embryonic stem cells for basic research and cell replacement therapies. The findings highlight a major challenge in developing clinical and scientific applications for the powerful new technique of making iPS cells, which, like embryonic stem cells, have the capacity to differentiate into any type of cell in the body. We found iPS cells retain a 'memory' of their tissue of origin. iPS cells made from blood are easier to turn back into blood than, say, iPS cells made from skin cells or brain cells. In contrast, another technique known as nuclear transfer creates pluripotent stem cells without apparent memory and equally adept at transforming into several tissue types. In iPS cells, the memory of the original donor tissue can be more fully erased with additional steps or drugs, the researchers found, which made those iPS cells as good as the nuclear-transfer stem cells at generating different types of early tissue cells in lab dishes. The residual cellular memory comes in part from lingering genome-wide epigenetic modifications to the DNA that gives each cell a distinctive identity, such as skin or blood, despite otherwise identical genomes. In the study, the persistent bits of a certain type of epigenetic modification called methylation were so distinctive in iPS cells that their tissues of origin could be identified by their methylation signatures alone. We found the iPS cells were not as completely reprogrammed as the nuclear transfer stem cells. Namely, DNA methylation was incompletely reset in iPS cells compared to nuclear transfer stem cells. Further, the residual epigenetic marks in the iPS cells helped to explain the lineage restriction, by leaving an epigenetic memory of the tissue of origin after reprogramming. These findings cut across all clinical applications people are pursuing and whatever disease they are modeling. Our data provide a deeper understanding of the iPS platform. Everyone working with these cells has to think about the tissues of origin and how that affects reprogramming.

Scientific Abstract:
Somatic cell nuclear transfer and transcription-factor-based reprogramming revert adult cells to an embryonic state, and yield pluripotent stem cells that can generate all tissues. Through different mechanisms and kinetics, these two reprogramming methods reset genomic methylation, an epigenetic modification of DNA that influences gene expression, leading us to hypothesize that the resulting pluripotent stem cells might have different properties. Here we observe that low-passage induced pluripotent stem cells (iPSCs) derived by factor-based reprogramming of adult murine tissues harbour residual DNA methylation signatures characteristic of their somatic tissue of origin, which favours their differentiation along lineages related to the donor cell, while restricting alternative cell fates. Such an 'epigenetic memory' of the donor tissue could be reset by differentiation and serial reprogramming, or by treatment of iPSCs with chromatin-modifying drugs. In contrast, the differentiation and methylation of nuclear-transfer-derived pluripotent stem cells were more similar to classical embryonic stem cells than were iPSCs. Our data indicate that nuclear transfer is more effective at establishing the ground state of pluripotency than factor-based reprogramming, which can leave an epigenetic memory of the tissue of origin that may influence efforts at directed differentiation for applications in disease modelling or treatment.